A Novel Triple Medicine Combination Injection for the Resolution of Keloids and Hypertrophic Scars

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ABSTRACT

Keloids and hypertrophic scars remain one of the more difficult treatment concerns for clinicians. A variety of therapies have been used in the past with moderate success. On occasion, combination therapy has been used to treat these lesion, in an attempt to lessen the symptoms of pain and pruritus that often accompanies keloids and hypertrophic scars, as well as treating the actual lesions themselves. A novel triple combination injection process is introduced here in an attempt to further reduce the signs and symptoms of these lesions. The combination includes 5-fluoruracil, triamcinolone acetonide, and hyaluronidase. All three work in concert to treat keloids and hypertrophic scars, and this is the first work at looking at these medicines given together, at the same time, in a series of recalcitrant keloids and hypertrophic scars. The positive results warrant further investigation and hope for those with keloids and hypertrophic scars. (*J Clin Aesthet Dermatol.* 2014;7(11):31–34.)

Keloids and hypertrophic scars are some of the most troublesome of all benign growths on the human body to treat for clinicians. Those affected with keloids and hypertrophic scars often consult dermatologists with symptoms of pain and pruritus, especially when these symptoms are of severe intensity. In some cases of these skin lesions, they can be the cause of disharmony in both social and interpersonal relations. For these reasons, it is imperative that we find solutions to treat these lesions that resolve the symptoms and treat the actual lesions.

Keloids, as has been reported,[1] have been shown to be composed of large, thick collagen fibers of both types I and III collagen. In addition, the fibroblasts that are present in keloids tend to persist longer than those of normal skin and have been shown to exhibit a fourfold increase in fibronectin synthesis. This affects the overall healing of the scar.[2]

Many therapeutic agents have been used for the treatment of keloids and hypertrophic scars. Treatment guidelines and recommendations have been previously published.[1] One of the interesting notions that have been brought out in many clinical studies is that recurrence, no matter what the treatment, is common with monotherapy. Combination therapy may provide us with an opportunity to increase these response rates and achieve a desirable result in dealing with these lesions.

By happenstance, the authors' clinic began with the idea of combining injectable 5-fluorouracil (an antimetabolite that suppresses fibroblast proliferation), triamcinolone acetonide (an anti-inflammatory agent), and hyaluronidase (an agent that has been shown to dissolve fibrous bands). All of these agents have been tried either individually or in combination of two of the agents in earlier clinical studies with somewhat encouraging results.[1] In that study, the authors found that the use of injectable 5-fluorouracil and triamcinolone acetonide was statistically significant in reducing the signs and symptoms of the keloids and hypertrophic scars as compared to intralesional triamcinolone acetonide alone.[3]

DISCLOSURE: The formulation for the triple combination injection is copyright protected by the principal author. The authors have not received any grants or support of any other kind for conducting the injection treatments on their patients.

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Figure 1. Three-year-old keloid on the chest of a young man pretreatment

Figure 2. Complete flattening of keloid after four monthly injections of triple combination therapy (5-fluoruracil, triamcinolone acetonide, and hyaluronidase)

To date, this is the first report of using these three agents together to determine if there is increased efficacy.

METHODS

Twenty patients presenting with either keloids or hypertrophic scars to the dermatology clinics at Bombay Hospital and Lilavati Hospital in Mumbai, India, were selected to participate in this clinical evaluation. The majority of these patients had their scars previously injected with intralesional corticosteroids (triamcinolone acetonide) with no long-lasting benefit, i.e., recurrence of associated symptoms of pain or pruritus. All of the patients entered into this evaluation with pain and/or severe pruritus prior to inclusion into the clinical study. The rationale behind using this novel triple combination injectable formula was explained to each of the patients, and informed consents were obtained.

A detailed medical history was taken at the initial screening and treatment visit. In particular, the duration of each of the scars to be treated and the causative event leading to the formation of the scar were captured. Specific attention was also given to past medical therapy for the scars that were going to be treated, any concomitant medications being utilized, as well as any drug allergies, all of which were recorded in the medical records.

Patients were informed that multiple injection sessions would be required, which were planned for one-month intervals. On average, patients required three treatment sessions to achieve a significant result in reducing their lesions and associated symptoms. At each visit, a dermatologist assessed the keloids and hypertrophic scars and the individual lesions were photographed. Each patient also completed a verbal patient satisfaction survey at every visit.

The novel triple combination injectable chosen for this evaluation was made from three known actives in treating hypertrophic scars and keloids. A total 1mL solution was prepared of the combination by aspirating 0.6mL from a 5mL ampoule of 5-fluorouracil (250mg/5mL) and 0.4mL from a 1mL vial of triamcinolone acetonide 40mg/mL. These were then injected into a vial containing a vacuum dried tablet of ovine origin hyaluronidase 1500 units. The vial, with the three agents incorporated, was shaken vigorously for several minutes to assure adequate mixing of the components. The mixture was then aspirated into a 2mL syringe with an 18-gauge needle.

The keloids and hypertrophic scars were then cleaned with an alcohol swab. The triple combination mixture was injected into the body of the scar utilizing a 26-gauge needle. Patients with larger or with multiple scars required more than one 1mL injections at each of their visits to cover the entire affected scar area.

RESULTS

All patients tolerated the triple combination injection well. Pain, varying from mild to moderate, was experienced at the time of injection in the majority of the patients; none of the patients discontinued the study as a result of pain upon injections. The pain lasted upwards of four hours post-injection. Patients were advised to take appropriate medications (nonsteroidal anti-inflammatory drugs) and to apply ice over the treated scars. Three of the patients experienced a superficial skin ulceration and scabbing of the scar where an excess of the solution was injected. These resolved without any significant sequelae.

Each patient was evaluated at monthly intervals when the treated scar was photographed. Pre- and post-treatment photographs of two of the patients with keloids are shown in Figures 1 to 4. The first patient (Figures 1

Figure 3. Keloids of 17 years' duration on chest following acne in a middle aged man pretreatment

Figure 4. Shrinking of keloids after four monthly injections of triple combination therapy (5-fluoruracil, triamcinolone acetonide, and hyaluronidase)

and 2) presented with a painful and pruritic keloid on the chest. The scar had been present for three years before presentation to the dermatology clinic. The patient underwent two sessions of intralesional corticosteroid injections with no change in the keloid or its associated symptoms. The patient underwent four sessions of injections with the triple combination formula with flattening of the keloid itself and resolution of the associated pain and pruritus. The second patient (Figures 3 and 4) presented with multiple keloids on the chest that had been present since his teenage years. Over the years, he underwent treatment with intralesional corticosteroids, which seemed to decrease the symptoms of pain and pruritus and actually had some benefits in scar shrinkage, but the scars reverted back to their original form once the therapies had stopped. The patient underwent four monthly sessions with the triple combination intralesional therapy. He is now one-year post his fourth injection and the pain and pruritus are resolved and the keloids are flatter than the baseline.

DISCUSSION

The rationale for utilizing a triple combination formula for the treatment of keloids and hypertrophic scars is rather straightforward. Each of the ingredients chosen has a positive effect on reducing the symptoms sometimes associated with these difficult-to-treat skin lesions. When taken together, these ingredients minimize the multiple injections necessary if they were to be administered on an individual basis.

Triamcinolone acetonide has long been the steroid of choice for the injectional medicine in the treatment of hypertrophic scars and keloids. Most of the clinical research in the scar arena suggests that intralesional corticosteroids, alone, or in combination, provide the best relief of local symptoms as well as flattening of the scars themselves. The use of intralesional corticosteroids has resulted in varying degrees of success, but also has a side effect profile that always needs to be kept in mind, in the form of skin atrophy, telangiectasias on the skin, and skin pigmentary changes.[1] These side effects may have resulted in part due to larger amounts of the drug required in treating the scars to get to the desired outcome. None of the patients in this evaluation developed any of the side effects described above, as the quantity of triamcinolone given to each patient was much smaller.

5-fluorouracil injections into keloids have been shown to be very effective in reducing the size of keloids, but are often associated with severe pain and possibly ulceration at the site of injection. Systemic absorption has been reported following the injection and may cause anemia, leukopenia, and thrombocytopenia.[4] However, used in combination with other agents enables clinicians to use a smaller dose for each injection, resulting in better acceptability with no reported systemic side effects.

Hyaluronidase, the third ingredient the authors have been using in the triple combination formula, has been used for many years in intra-abdominal surgical procedures[2,5]; ear, nose, and throat surgical procedures[6]; and even in spinal surgeries[7] to break through tough fibrous adhesions. Keloids have excessive amounts of collagen that are layered down haphazardly into the dermis. These "whirls" were found to dissolve very well when hyaluronidase injections were given to patients along with the triamcinolone acetonide and 5-fluorouracil in those who were evaluated.

In addition, all of the patients felt that the skin associated with the scar was softer following the injections, and the injectors noted that subsequent injections were "easier" to administer than the first injections.

CONCLUSION

The novel triple combination injection has been shown in this clinical evaluation to be promising and long lasting for the suppression of symptoms related to keloids and hypertrophic scars. In comparison to some surgical procedures and other modalities, this therapy is rather inexpensive, easily available, and an effective treatment option that can be offered in the consulting/treatment room. However, in order to verify that these results are in fact accurate, we suggest that a randomized, multi-armed clinical trial be carried out to determine how well this triple combination therapy works in comparison to all the individual parts.

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